U.S. FOOD & DRUG ADMINISTRATION

Combination Products: Updates and Best Practices

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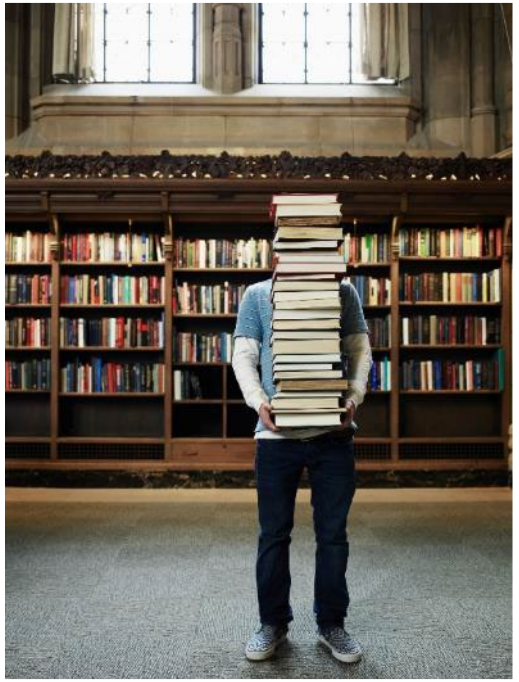
CDER | US FDA


LIBRARY



Learning Objectives

Overview of FDA Review of Combination products

Combo Product Updates

Best Practices for Submissions and Agency Engagement

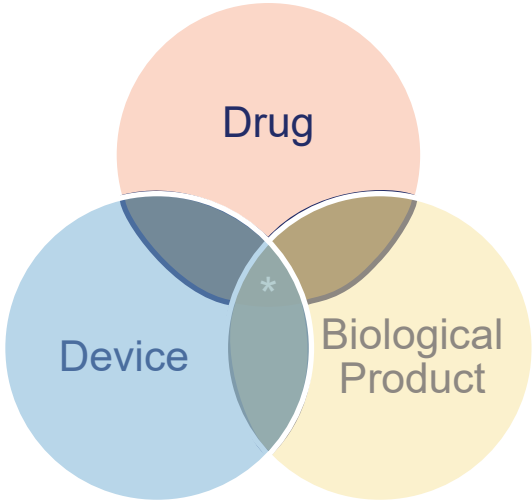
Overview of FDA Review of Combination Products

- Combination product definition
- Center assignment
- Premarket Review of Combos

What is a Combination Product?

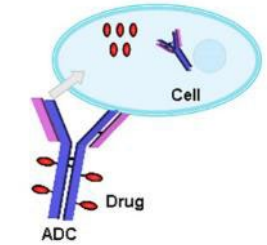
- Composed of 2 or more **DIFFERENT** type of medical products
  - A drug, device or biological product in a combination product is referred to as a "constituent part." (21 CFR 4.1)

- 21 CFR 3.2(e)
  - Combined physically or chemically into a single entity ("single-entity")
  - Co-packaged / Kit ("co-packaged")
  - Sold separately, but labeled for use together ("cross-labeled)



Types of Combination Products

	“Single-entity”
Description	Chemically or physically combined constituent parts
Examples	• Prefilled syringe • Transdermal patch • IV bags prefilled with drugs • Antibody-drug conjugates • Metered-dose inhaler
Reference	21 CFR 3.2(e)(1)



Antibody–Drug Conjugate (ADC)

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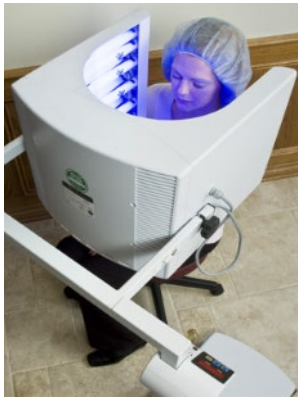
6

Types of Combination Products

	"Co-packaged"
Description	Constituent parts packaged together
Examples	• First-aid or surgical kit • Syringe packaged with vial of drug • Drug + syringe prefilled with diluent, reconstitution / transfer device, fillable cartridge
Reference	21 CFR 3.2(e)(2)

Types of Combination Products

	“Cross-labeled
Description	Constituent parts separately packaged / sold labeled for use together
Examples	• Reusable light source and one time use photoactivated
Reference	21 CFR 3.2(e)(1)



CHOOSE YOUR OWN ADVENTURE

Combination Product Assignment

Primary Mode of Action (PMOA) (21 CFR 3.2(m))

"the **single mode of action** of a combination product that **provides the most important therapeutic action** …"

Example: If PMOA is drug, product is assigned to CDER

Assignment Algorithm (21 CFR 3.4)

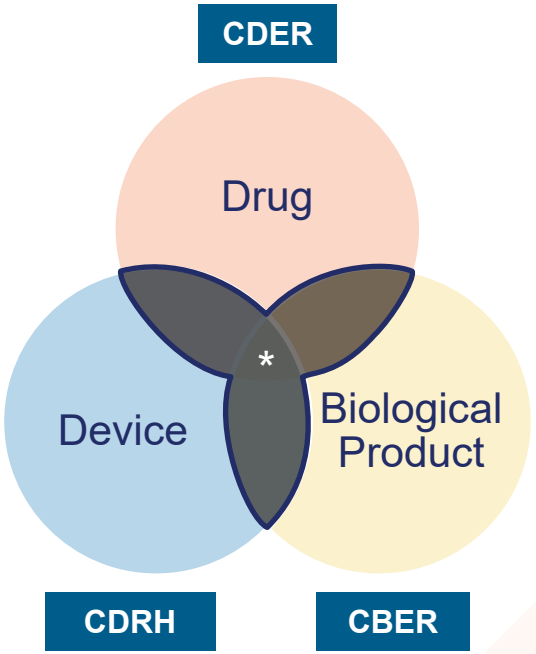
PMOA cannot be determined with reasonable certainty

- **Tier 1: Consistency**

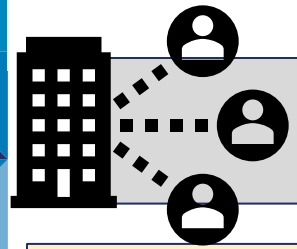
Assign the product to the Center that regulates other combination products that present similar questions of safety and effectiveness.

- **Tier 2: Expertise**

When Tier 1 does not apply, assign the product to the Center with the most expertise related to the most significant safety and effectiveness questions



Premarket Review of Combo Products



FDA assesses the safety and effectiveness of the combination product as a whole.

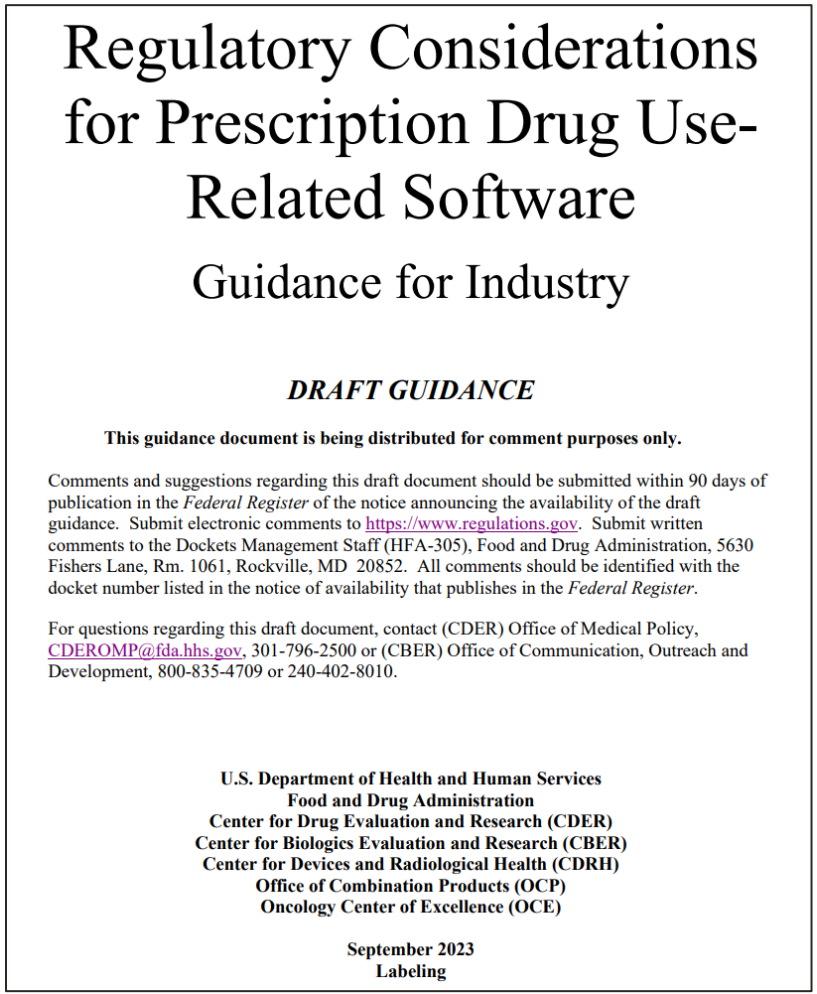
Lead Center for the combo product

- Serves as Sponsor's primary point of contact
- Lead center's processes and procedures are used (e.g., meetings, applications)
- Engages expertise in other centers via the Inter-center consult request process.

CDER	CDRH	CBER
IND NDA BLA ANDA	IDE 510(k) PMA HDE	IND/IDE BLA PMA 510(K) NDA (rare!)

Combo Product Updates

- Guidance: Regulatory Considerations for Prescription Drug Use-Related Software (DRAFT)
- Artificial Intelligence and Medical Products
- Guidance: Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4 Guidance for Industry (Immediate Implementation)
- Guidance: Application of Human Factors Engineering Principles for Combination Products: Questions and Answers
- Guidance: Controlled Correspondence Related to Generic Drug Development



Regulatory Considerations for Prescription Drug Use-Related Software

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Medical Policy, CDEROMP@fda.hhs.gov, 301-796-2500 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)
Oncology Center of Excellence (OCE)

September 2023
Labeling

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https://www.fda.gov/media/172165/download

Regulatory Considerations for Prescription Drug Use-Related Software (PDURS) – Draft Guidance

Prescription **D**rug **U**se **R**elated **S**oftware (PDURS) generally includes software that

(1) is disseminated by or on behalf of a drug sponsor, *and*

(2) produces an end-user output that supplements, explains, or is otherwise textually related to one or more of the sponsor's drug products, regardless of whether the software is a device.

PDURS Draft Guidance

The guidance describes:

- How FDA intends to apply its drug labeling authorities to certain software outputs
- Factors that FDA intends to analyze to determine whether the end-user output should be treated as FDA-required labeling or promotional labeling
- Whether the corresponding software function should be described in the PI, and if so, how it should be described.
- When and how sponsors should submit end-user output to FDA.

Drug Labeling

- Required:
  - For prescription drugs and biological products, FDA-required labeling is the labeling, drafted by the manufacturer, that is reviewed and approved by FDA.
  - It includes the information that is essential for a provider to make an informed decision about the risks and benefits of prescribing the drug for a patient and the information needed to safely and effectively use the drug.
- Promotional:
  - Promotional labeling is generally any labeling other than FDA required labeling that is devised for promotion of the product.
  - Promotional labeling can include printed, audio, or visual matter descriptive of a drug that is disseminated by or on behalf of a drug's manufacturer, packer, or distributor.

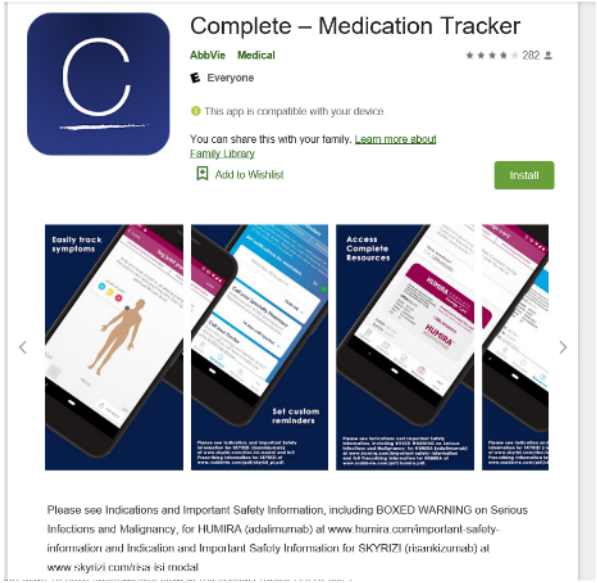
Highlights from Draft Guidance

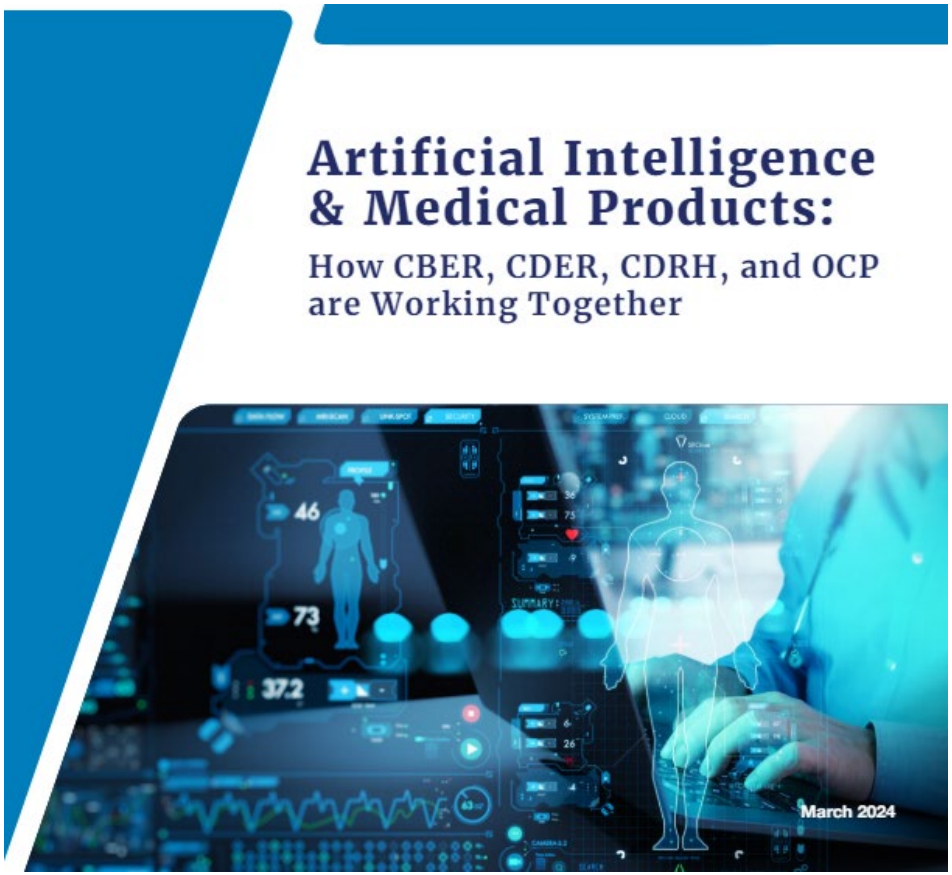
- Independent of device status
- FDA required labeling vs promotional labeling considers:
  - Function essential to safe/effective use of product
  - Evidence of clinical benefit
  - Relies on data transferred directly from a device constituent of a combo product
- When/how to submit PDURS information to FDA
- Does not apply to software developers that are not affiliated with the drug sponsor

PDURS Considerations for Devices

- Output could be PDURS but the software may meet the definition of a device
- PDURS may be submitted under a device marketing submission.
- CDRH's review will include considerations raised related to representations about the drug in consultation with CDER or CBER. Under draft guidance:
  - If submitting a CDRH marketing application, then form 2253 not needed
  - If making changes to PDURS and a new 510(k) is not needed, then Form 2263 is needed
  - Form FDA 2253 is not a replacement for device marketing submission requirements for a device modification.

Examples of PDURS





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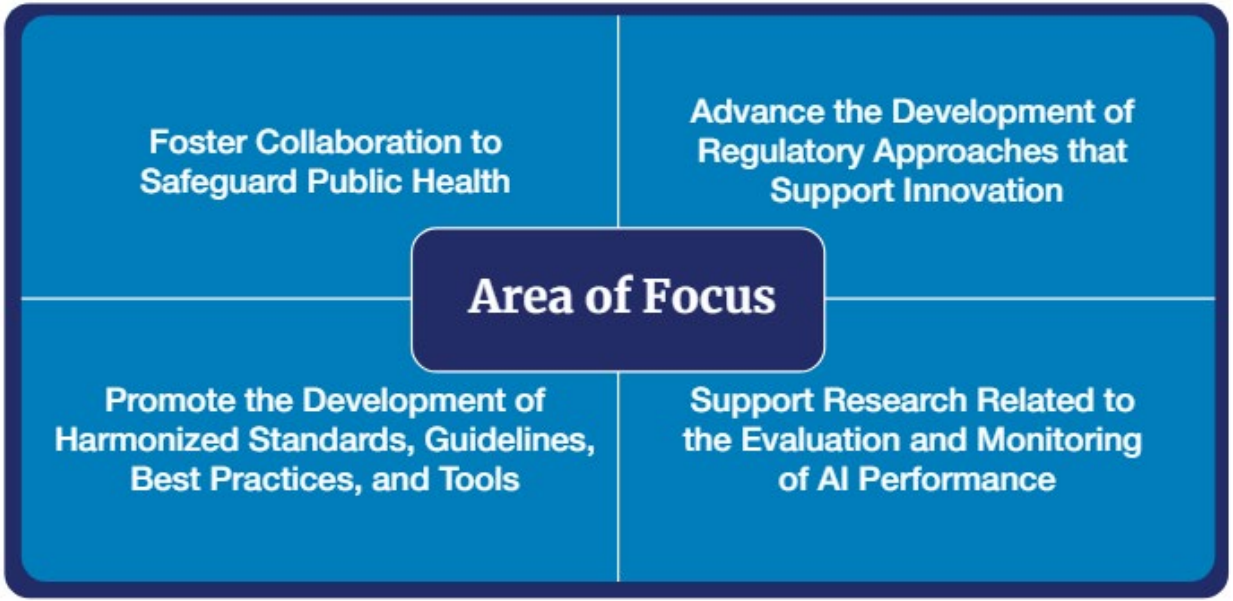
AI and Medical Products



Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact the office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Combination Products (OCP)

March 2022
Combination Products

https://www.fda.gov/media/157067/download

Genus Decision and 21 CFR 200.50(c)

- Genus in brief
  - Barium sulfate contrast imaging agents are used to improve visualization of the gastrointestinal tract in radiographic diagnostic studies
  - Loss of discretion to regulate devices as drugs
  - Congress later clarified in Section 503 of the FD&C Act that any contrast agent, radioactive drug, or OTC monograph drug shall be deemed to be a drug under section 201(g) and not a device under section 201(h).

https://law.justia.com/cases/federal/appellate-courts/cadc/20-5026/20-5026-2021-04-16.html

Why does this impact 21 CFR 200.50?

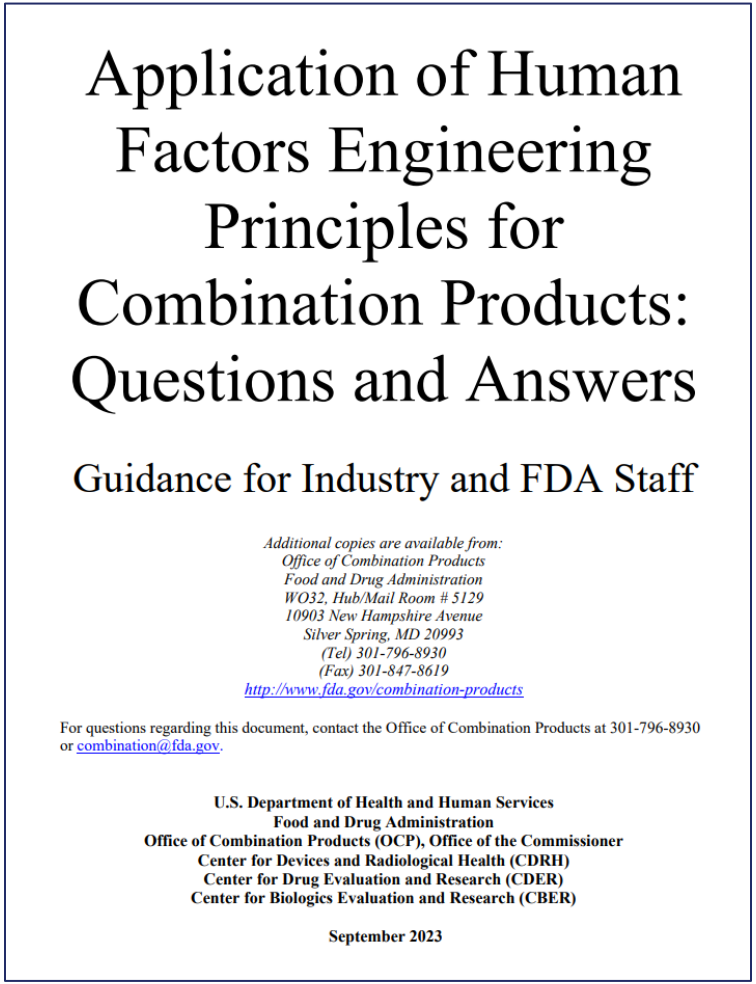
- Devices packaged with drugs are regulated as drug-device combination products
  - *Exception*: 21 CFR 200.50(c): **Eye cups, eye droppers, and other dispensers intended for ophthalmic use** should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. **These articles, which are regulated as drugs if packaged with the drugs with which they are to be used**, should be packaged so as to maintain sterility until the package is opened and be labeled, on or within the retail package, so as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use.
- Post-Genus: Eye cups, eye droppers, and other dispensers intended for ophthalmic use are **now regulated as drug-device combination products**

Guidance: Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4

- Gave a 12 month period where FDA did not intend to take action with respect to ophthalmic products that were not previously regulated as combination products because of the now obsolete language in § 200.50(c) regarding 21 CFR part 820 and postmarketing requirements.
  - Period ended March 2023
- For lower-risk device constituent parts, eye dropper bottles/ampules that administer the drug directly to the eye, we are evaluating the application of part 820 quality system (QS) requirements to combination products and generally do not intend to take action with respect to noncompliance with any applicable part 820 requirements for these ophthalmic products.
  - When we publish our current thinking it will include timing expectations

Ophthalmic Devices Panel Meeting

- Ophthalmic Devices Panel of the Medical Devices Advisory Committee for the Food and Drug Administration met on November 10, 2022 to discuss and make recommendations on the classification of ophthalmic dispensers, which are currently unclassified preamendment devices, to class I (general controls).
  - Discussed FDA's proposed classification of Class I for ophthalmic dispensers under the product code "LXQ."
  - This included a discussion of the known risks and safety/effectiveness concerns and a general classification recommendation for ophthalmic dispensers.
  - Recommended that ophthalmic dispensers indicated for use to irrigate the eye or provide controlled instillation of ophthalmic medication dropwise to the eye be regulated as Class I [510(k) exempt] devices; not GMP exempt



Application of Human Factors Engineering Principles for Combination Products: Questions and Answers

Guidance for Industry and FDA Staff

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room # 5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/combination-products

For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP), Office of the Commissioner
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023

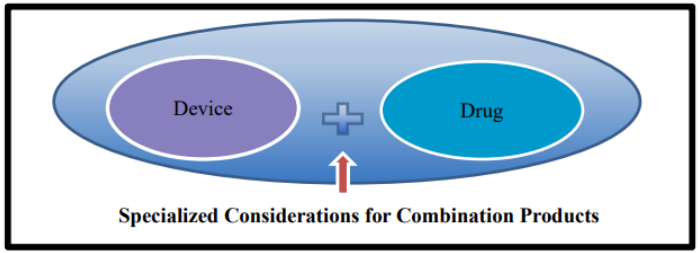
https://www.fda.gov/media/171855/download

Application of Human Factors Engineering Principles for Combination Products: Questions and Answers (Final Guidance)

- Not meant to replace CDRH or CDER human factors (HF) guidance
- Information in a question-and-answer format
- Clarifies how the unique aspects of a combination product influence the considerations within the human factors engineering (HFE) process

HF for Combos Guidance

- A key goal of applying HFE principles during development is to ensure that the user interface supports the safety and effectiveness of the combination product as a whole
- Should consider use-related risks associated with the combination product as a whole that do not exist for the device alone or drug alone

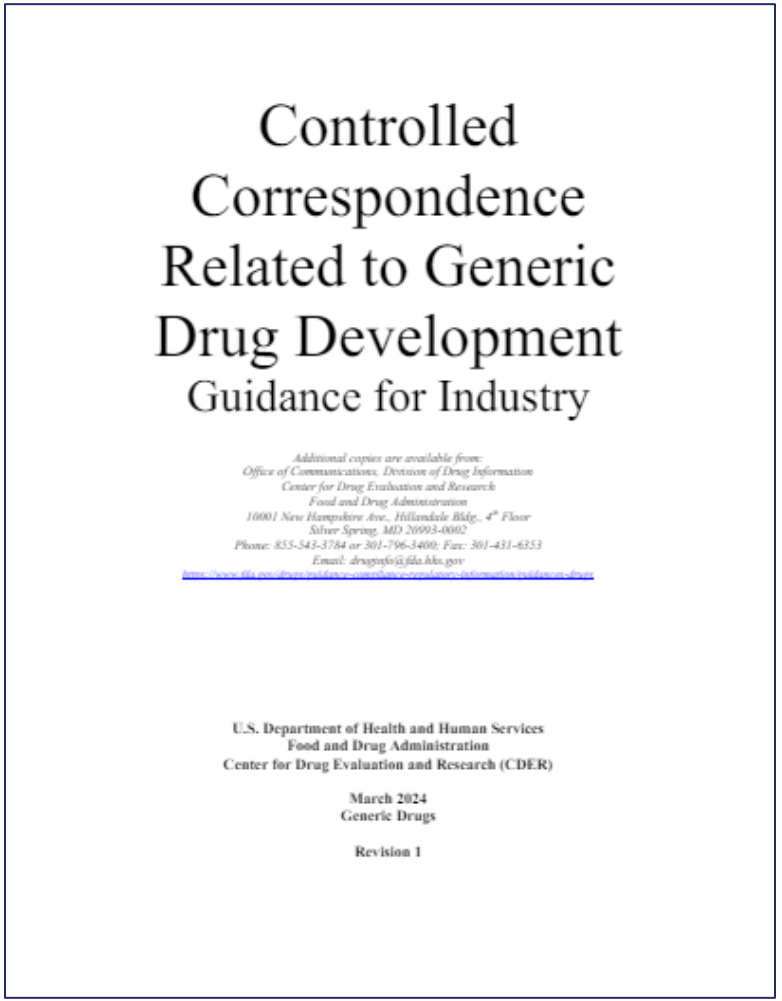


- The user interface for a combination product includes all points of interaction between the combination product and the user(s), including displays, controls, packaging, product labels, carton labeling, instructions for use, and training, if applicable

HF for Combos Guidance

Q & A includes items such as:

- Key definitions, such as “final finished combination product” and “combination product critical task”
- How to identify combo product critical tasks
- How FDA evaluates HF validation study results
- Difference between use-related risk analysis (URRA) and other risk analysis
- HF actual-use validation study vs other studies
- Timing for HF validation studies



Controlled Correspondence Related to Generic Drug Development

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2024
Generic Drugs

Revision 1

https://www.fda.gov/media/164111/download

Controlled Correspondence Related to Generic Drug Development

- Provides information regarding the process by which generic drug manufacturers can submit to FDA controlled correspondence requesting information related to generic drug development
- Provides additional detail and recommendations concerning what inquiries FDA considers to be controlled correspondence and what information requestors should include
- Requests related to the evaluation of the user interface of a drug-device combination product
- Requests related to device performance and specifications
- Submit separate controls for questions related to separate elements of generic drug development or that require review by more than one discipline or Center

Engaging FDA on Combo Products

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Best Practices for Engaging with FDA

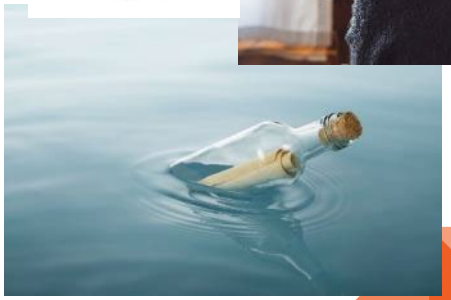
If combination product status or jurisdiction is not clear, consider a pre-RFD or RFD to the Office of Combination Products (OCP). Alternatively, engage with the Center Product Jurisdiction Officers (PJOs) for confirmation. **A pre-RFD or RFD is NOT needed for most products.**

PRE-RFD	RFD
• Non-binding decision • Often helpful during for early development products • Interactive process • No page limit • Response goal is 60 days • Less information needed • Guidance: How to Prepare for a Pre-Request for Designation	• Binding decision • Well characterized configured products • Non-interactive process after RFD is filed • 15-page limit • Letter is issued within 60 days • Requirements in 21 CFR 3.7 • Guidance: How to write a Request for Designation (RFD)

Best Practices for Engaging with FDA

Use Center-based mechanism(s) of LEAD CENTER to request feedback:

- CDRH - "Q-Submission Program"
- CDER - Formal meeting guidance for:
  - PDUFA Products
  - BsUFA Products
  - GDUFA – Complex Products and Product Specific Guidance (PSG)
- CDER/CBER/CDRH - Requesting FDA Feedback on Combination Products



Best Practices for Engaging with FDA

- Submit all meeting requests to the lead Center, even if all questions are related to the non-lead Center constituent part
- All communications through the assigned point-of-contact
- Clearly identify product as a combination product

Best Practices for Engaging with FDA

- Ask specific questions appropriate for the stage of development
- Provide sufficient information for FDA to consider
- Identify whether a constituent part is being used in other development programs – may be able to leverage information from another submission
- For device constituents in drug-led combination products, identify 510(k) or PMA number if already authorized for marketing

FDA will:

- Identify primary point of contact
- Provide timely communication
- Engage relevant expertise, including from other Centers
- Provide comprehensive feedback representing current thinking
- FDA will generally include requested staff, when appropriate
  - Sponsor's may request OCP and/or Center PJO staff attend

Challenge Question 1

You are developing a novel implantable device that is prefilled with a drug that was already approved for the same indication ten years ago, but without the device. Which Center is responsible for the combination product?

- CDER
- CDRH

Challenge Question 2

If you have an approved combination product in CDER (e.g., NDA), who should you ask about the type of supplement needed for making a change to the device constituent of the combination product?

a) OCP

b) CDER

c) CDRH

fda.g

Keep calm and ask FDA:

- Kristina Lauritsen, PhD – Kristina.Lauritsen@fda.hhs.gov
- Center Combo/PJO teams:
  - CDER CDERProductJurisdiction@fda.hhs.gov
  - CDRH CDRHProductJurisdiction@fda.hhs.gov
  - CBER CBERProductJurisdiction@fda.hhs.gov
- Office of Combination Products – combination@fda.gov

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